Body mass index and all-cause mortality in heart failure with normal and reduced ventricular ejection fraction - a dose-response meta-analysis

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Abstract

Background

For patients with heart failure, there is an inverse relation between body mass index (BMI) and mortality, sometimes called the obesity-paradox. However, the relationship might be either U- or J-shaped and might differ between patients with reduced (HFrEF) or preserved left ventricular ejection fraction (HFpEF). We sought to investigate this further in a dose-response meta-analysis of published studies.

Methods

PubMed and Embase from June 1980 to April 2017 were searched for prospective cohort studies evaluating associations between BMI and all-cause mortality in patients with HFrEF (LVEF <40%) or HFpEF (LVEF ≥ 50%). Summary estimated effect sizes were obtained by using a random effects model. Potential non-linear relationships were evaluated by using random effects restricted cubic spline models.

Results

Ten studies were identified that included 96,424 patients of whom 59,263 had HFpEF (mean age 68 years of whom 38% were women) and 37,161 had HFrEF (mean age 60 years of whom 17% were women). For patients with HFpEF, the summary hazard ratio (HR) for all-cause mortality was: 0.93 (95%CI: 0.89-0.97) per 5 units increase in BMI (I-squared = 75.8%, p for heterogeneity = 0.01 and Begg's test, p = 1.0, Egger's test, p = 0.29) but the association was U-shaped (p for nonlinearity <0.01) with the nadir of risk at a BMI of 32-33 kg/m². For patients with HFrEF, the summary HR for all-cause mortality was: 0.96 (95%CI: 0.92-0.99) (I-squared=95%, p for heterogeneity < 0.001 and Begg's test, p=0.45, Egger's test, p=0.01). The relationship was also U-shaped (p < 0.01), although 'flatter' than for HFpEF, with the nadir at a BMI of 33 kg/m².

Conclusions

For patients with heart failure, the relation between BMI and mortality is U-shaped with a similar nadir of risk for HFpEF and HFrEF at a BMI of 32-33 kg/m². Whether interventions that alter weight in either direction can alter risk is unknown.

Introduction

Many studies have shown that mild-to-moderate obesity is associated with a lower mortality amongst patients with heart failure: the so-called obesity-paradox. [1-5] The possible causes of the paradox are controversial. There is no doubt that BMI declines as heart failure (HF) becomes more severe: some believe that a low BMI simply reflects more advanced disease. Adherents of this view suggest that interventions to reduce a high BMI will benefit patients symptomatically and perhaps prognostically, by reducing pro-inflammatory visceral adiposity and perhaps haemodynamic stress as well as improving glycaemic control.[6] Others believe that a higher BMI may provide a metabolic reserve as disease progresses or even be intrinsically beneficial, in which case efforts should be made to increase rather than reduce BMI. Indeed, one of the great successes of heart failure therapy, beta-blockers, increases BMI.[7]

A recent study from the MAGGIC[8, 9] collaboration, based on individual patient data, reported that there was a U-shaped relationship between BMI and all-cause mortality both for patients with HFpEF and those with HFrEF with the nadir of risk at a BMI of 30-34.9 kg/m². In order to investigate this observation further, we conducted a systematic review and dose-response meta-analysis to quantify and better understand the potential non-linear relation between BMI and prognosis in prospective cohort studies of patients with HFpEF and HFrEF.

Methods

Search Strategy

The study was designed according to the Meta-analysis of Observational Studies in

Epidemiology (MOOSE) Group and the PRISMA 2009 guidelines.[10, 11] We searched for all prospective cohort and other related studies that evaluated the associations between BMI and all-cause mortality in patients either with heart failure and a reduced (HFrEF; LVEF <40%) or preserved ejection fraction (HFpEF; LVEF ≥ 50%). Only studies with at least three categories of BMI were considered.[12] Studies[13-15] with patients with a mean left ventricular ejection fraction (LVEF) close to 45% were not included as the patients could not be reliably classified as having predominantly HFpEF or HFrEF. To reduce bias, only prospective cohort studies were included, including an individual patient-data meta-analysis.[8]

PubMed and Embase from June 1980 to April 2017 were searched evaluating associations between BMI and all-cause mortality in patients with HFrEF or HFpEF. There were no language restrictions. Search terms included: HFpEF, HFrEF, HFnEF, reduced, normal or preserved EF, reduced, normal or preserved ejection fraction, BMI, body mass index, mortality and death. We also searched reference lists of the retrieved articles to identify other eligible studies. Two investigators independently reviewed all titles and abstracts from the search results to identify articles that met the inclusion criteria. Selected studies were compared, and disagreement was resolved by discussion and consensus. If any of the eligibility criteria were not met, the article was excluded. If results were incomplete or unclear, attempts were made to contact the study authors. Articles finally selected for review were checked to avoid inclusion of data published in duplicate. Relevant information was collected on baseline characteristics, such as age, sex, New York Heart Association (NYHA) functional classification, HF phenotype, heart rhythm at baseline, mean follow-up and events.

Statistical Analysis

The hazard ratio (HR) with 95% confidence intervals for all-cause mortality in each baseline BMI category obtained from multivariable models for all studies was used as the effect size. A dose-response association between BMI and all-cause mortality was assessed by the methods described by Greenland and Longnecker[16] and Orsini[17] based on a generalized least squares regression model using STATA version 14.2. We assumed that the reference category was the lowest BMI category for each study. For studies in which the reference group was not the lowest category, we transformed it to the lowest category using the method proposed by Orsini.[18] We used the mid-point of the corresponding range of BMI as the exposure value. When upper and lower categories were open-ended, we used the width of the adjacent category to calculate an upper or lower bound.

For studies that did not report the number of person-years by BMI category, we used approximated values based on follow-up period, number of subjects provided and number of BMI categories. One study[19] reported results for peak oxygen uptake ≤14 and >14 $ml.kg^{-1}.min^{-1}$ separately; we combined the estimated hazard ratios using a fixed effect model to obtain an overall estimate. A potential non-linear relationship between BMI and mortality was evaluated by modelling BMI dose with the use of restricted cubic splines with 4 knots at fixed centiles (5%, 35%, 65% and 95%) based on all categories of BMI for all studies, and examined by testing the hypothesis that the regression coefficients of the spline transformations were all equal to zero. We produced a dose-response curve with a re-scaled reference category of BMI of 23.8 kg/m^2, which we took as a value within the normal weight range. Summary estimated effect sizes were obtained using a random effects model based on each study calculated using the method of Orsini et al.[20] Heterogeneity was assessed using Q test and I-squared statistics.[21] Forest plots were used to represent graphically the results generated from the random-effects meta-analysis. The pooled HR and the degree of

heterogeneity are presented. Publication-bias was minimized by comprehensive literature searching. In addition, Begg's test[22] and Egger's test[23] were used to investigate publication bias.

Results

The selection process and results are shown in **Figure 1**. Of 622 articles found by the initial search, 47 were retrieved for more detailed evaluation. Ten studies were identified with 96,424 patients, for whom the mean age was 64 years; 28% were women. The biggest study contained 47,866 patients[24] and the smallest study 446 patients.[25] Where NYHA class was reported, most patients were in class III or IV. One study included only women[26] and one study included predominantly (96%) men.[3]

Most studies were conducted in the United States of America (**Table 1**). Patients with a higher BMI were more likely to have a history of diabetes and hypertension, especially for patients with HFpEF. Patients with a BMI in the normal range were more likely to have IHD (**Table 2**). Patients with HFrEF were more likely to take digoxin (**Table 3**). Of the ten studies, nine reported all-cause mortality, three reported cardiovascular (CV) mortality and one reported death/urgent heart transplant/or ventricular assist device.[19]

HFpEF

Four studies[3, 8, 24, 27] including one individual patient data meta-analysis[8] included 59,263 patients of whom 6,061 died. The average patient age was 68 years, and 38% were women. In multivariable analysis, the variables most commonly adjusted for were: age, sex, LVEF,

diabetes, blood pressure, NYHA class, ischaemic aetiology and hypertension (**Table 4**). The summary HR per 5 unit increment in BMI was 0.93 (95%CI: 0.89-0.97) (I-squared = 75.8%, p for heterogeneity=0.01 (**Figure 2A**)), with an inverse association between BMI and all-cause mortality. There was no evidence of publication bias (Begg's test, p=1.0 or Egger's test, p=0.29). The dose-response meta-analysis showed a U-shaped association between BMI and all-cause mortality with the lowest mortality at a BMI of 32-33 kg/m^2 (p<0.01 for non-linearity, **Figure 3A**). Similar results were found when the MAGGIC meta-analysis[8] was excluded (leaving n = 53,210 patients). There were too few studies to investigate an interaction between age and mortality for patients with HFpEF (Table 5).

HFrEF

Seven studies were identified[8, 19, 25, 26, 28-30] with 37,161 patients of whom 12,429 died. The average patient age was 60 years and 17% were women. In multivariable analysis, the variables most commonly adjusted for were: age, sex, LVEF, diabetes, blood pressure, NYHA class, ischaemic aetiology and hypertension (**Table 4**). The summary HR per 5 unit increment in BMI was 0.96 (95%CI: 0.92-0.99) (I-squared = 95%, p for heterogeneity<0.001 (see **Figure 2B**)). There was no evidence of publication bias (Begg's test, p=0.45, Egger's test, p=0.01). The dose-response meta-analysis showed a 'flatter' U-shaped association than for HFpEF with the lowest mortality at a BMI of 32 kg/m^2 (p<0.01) (**Figure 3B**). Similar results were found excluding the MAGGIC meta-analysis[8] (leaving n= 21,205 patients). The negative relationship was statistically significant for patients with HFrEF who were aged ≥60 years (HR: 0.95 (0.92-0.97), p<0.05), but not for patients aged <60 years (HR: 0.97 (0.91-1.03), p>0.05), and the p-values for heterogeneity were different for each group (see Table 5). One study[30] showed a negative relation between BMI and CV deaths in patients with HFrEF

without giving detailed data. Another study[28] provided detailed data, and found a 'flatter' U-sharped relation between BMI and CV deaths than between BMI and all-cause mortality amongst patients with HFrEF (**Table 2**).

Discussion

This analysis confirms, in part, the existence of an obesity-paradox for patients with heart failure. However, rather than a linear relationship between greater BMI and longevity, we observed, as anticipated, a U-shaped relationship; very low body weight and extreme obesity are both known to be dangerous. Previous studies have reported a U-shaped relationship between BMI and mortality with a nadir anywhere between 30 kg/m^2 [26] and 42 kg/m^2.[31] Our analysis provides a considerably narrower range for the nadir of risk both for HFpEF and HFrEF at a BMI of 32-33 kg/m^2 although the U-shaped relationship was 'flatter' for HFrEF.

There are many possible explanations for the 'obesity-paradox' in patients with heart failure. Obesity may be a risk factor for developing heart failure at an earlier age; younger patients generally have a better prognosis.[32-35] Thus, so called "reverse-causation" could account for the relationship between obesity and prognosis. Obesity might induce symptoms, such as breathlessness on exertion or lying down, leading to earlier diagnosis of heart failure or even misdiagnosis. Obesity might indicate less advanced disease. Weight loss is an ominous sign in patients with heart failure even before patients become notably cachectic.[35-37] A recent report[38] suggested that patients with heart failure and a greater waist-hip ratio had a worse prognosis. This may reflect the pro-inflammatory response to accumulation of visceral/omental fat. Obesity is also associated with the development of type 2 diabetes that is

associated with an adverse prognosis in patients with heart failure. The proportion of patients with diabetes increases with BMI regardless of HF phenotype in all studies.

Alternatively, obesity might be protective. Fat might provide an energy reserve that helps a patient cope with the metabolic costs of illness, protecting muscle and bone from the catabolic effects of worsening heart failure. Fat might also provide protection against endotoxins.[39,40,41,42,8, 43,44,45] Treatment with beta-blockers causes BMI to rise and improves the prognosis of patients with HFrEF, although it is unclear whether this relationship is causal. However, ESC guidelines on heart failure no longer advise weight loss in moderately obese in patients.[46]

Many reports suggest an obesity-paradox for patients aged >50 years with established cardio-metabolic disease. This is true for hypertension[47], type-2 diabetes mellitus[48, 49], atrial fibrillation[50, 51] and ischaemic heart disease[52] as well as heart failure[53-55]. Reverse-causation could explain each instance. On the other hand, from a clinical perspective it is the prognosis of the patient who they are caring for that is important rather than the patient's prior medical history, which cannot be altered. Accordingly, knowing that a patient with heart failure who is slightly obese has a better prognosis might be helpful for making decisions about management. Patients might be advised to lose weight (and take more exercise) to improve symptoms and exercise capacity but whether this will have a beneficial or deleterious effect on longevity is unknown.

This is the first study using a dose-response meta-analysis to evaluate the association between BMI and all-cause mortality in patients with HFrEF and HFpEF. The advantage of using the

method is that it provides estimates that better quantify the potential non-linear relation between BMI and all-cause mortality. Another advantage of the approach is that it does not require the use of the same cut points for BMI in all studies, which means that all the BMI data can be used.

One problem in interpreting the data is the definition of HFpEF. Many people have "abnormal" features of diastolic function in association with increasing age and obesity. In the absence of conclusive evidence of cardiac dysfunction (such as atrial dilatation or raised plasma concentrations of natriuretic peptides), the diagnosis of heart failure is in doubt. Amongst the studies of HFpEF that we have included, only one (Haass et al.[27]) reported plasma concentrations of natriuretic peptides which, although raised, were much lower than typically seen in clinical trials of patients with HFrEF.

The study has several other limitations. Some patients with an LVEF of 40-49% (HFmrEF) will have been misclassified as either HFrEF or HFpEF. We did not include studies where the mean value for LVEF was around 45%[13, 15, 56] because it was not clear what proportion of these patients would have HFrEF or HFpEF. The characteristics and treatment of patients varied across cohorts as might be expected and differed in adjusted variables and follow-up time. We used a random effect model and most studies were controlled for age, sex, left ventricular ejection fraction, diabetes, blood pressure, NYHA class, ischemic aetiology and hypertension. We only included studies with BMI given in more than 2 categories, which potentially limits the number of studies. However, it makes more efficient for dose-response meta-analysis. In addition, weight changes in patients with heart failure, but the data are not

available from the studies included in our meta-analysis to investigate the relation between weight change and outcome.

The relation between BMI and outcome might depend on the end-point chosen. Patients with HFpEF are more likely to die from non-cardiovascular causes than are patients with HFrEF[57] but cause-specific mortality data were not available. Furthermore, no data are available to allow us to explore the effect of inflammation or dysglycaemia on the relation between BMI and survival.

Conclusion

Both for patients with HFpEF and HFrEF, the relationships between BMI and mortality are U-shaped with a similar nadir of risk at a BMI of 32-33 kg/m^2. Whether interventions to change BMI alter risk is unknown. Further research is required to discover the reasons underlying the obesity-paradox in heart failure and other cardio-metabolic diseases and to provide guidance on whether and how patients should attempt to lose or gain weight.

Figure legend

Figure 1: Flowchart of search process.

Figure 2: Adjusted relative risk (HR) for all-cause mortality per 5 units increment in BMI. (A): HFpEF; B): HFrEF). HR and 95% CI are represented by the black dot and horizontal line, respectively; the area of the grey square is proportional to the specific-study weight to the overall meta-analysis.

Figure 3: Association between BMI and all-cause mortality. A reference is set at BMI=23.8 (the top (A): HFpEF; the bottom (B): HFrEF). The middle boxes show the range of BMI for which the relative risk is <1.0 compared to the reference BMI.

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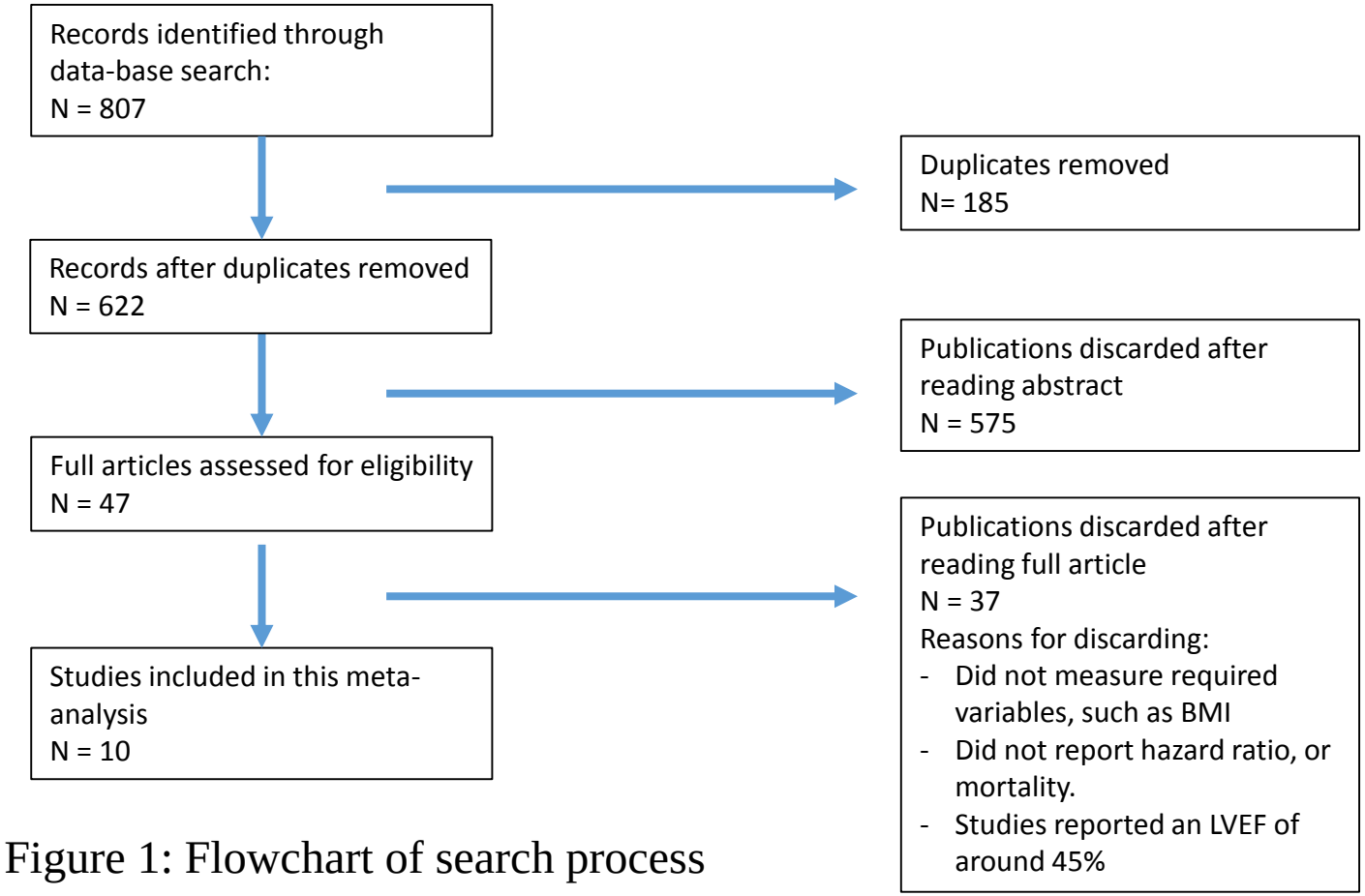
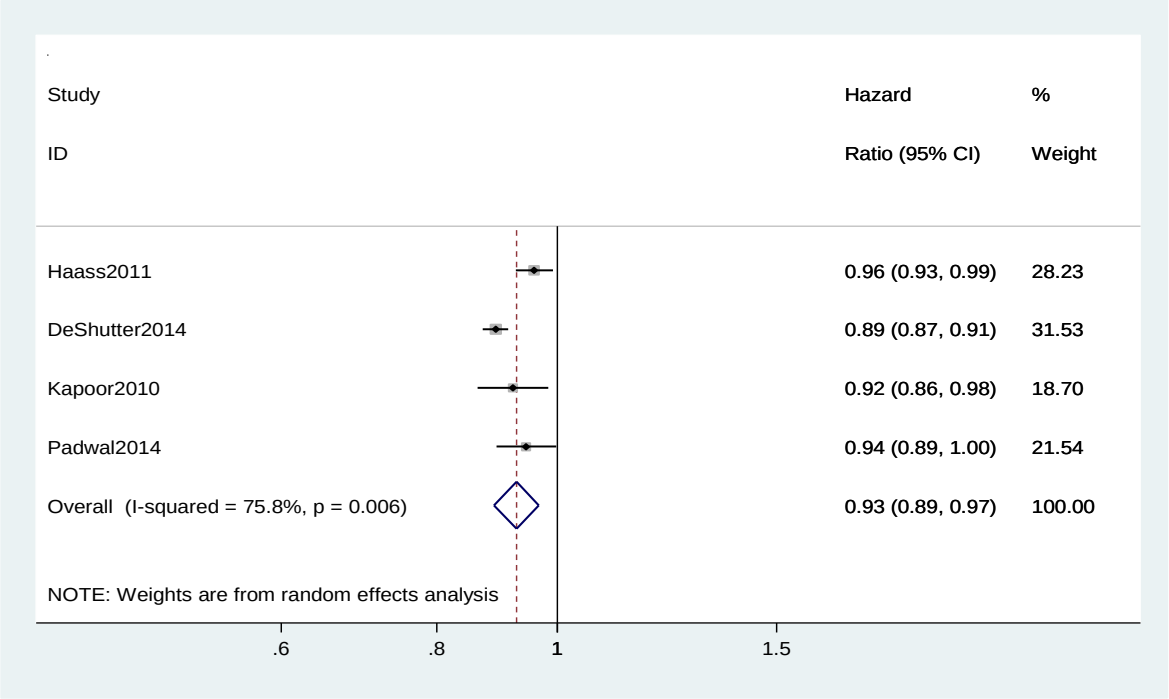


Figure 1: Flowchart of search process

A) HFpEF



B) HFrEF

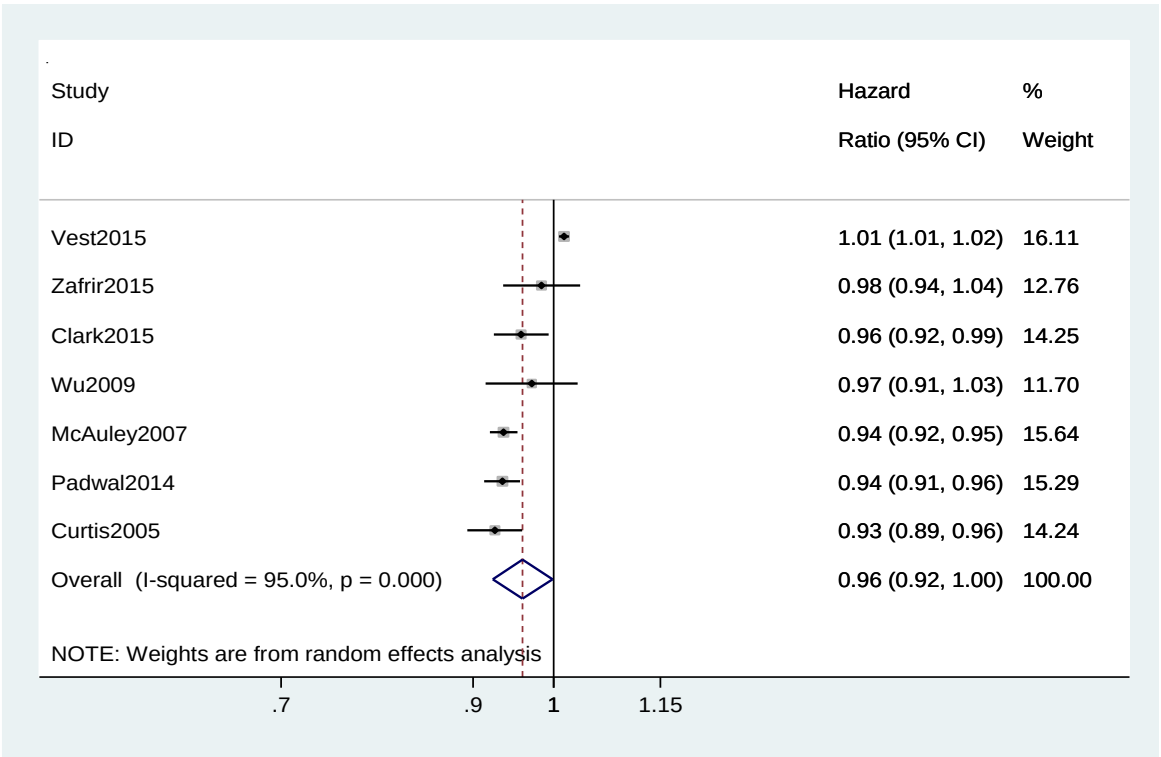


Figure 2: Adjusted relative risk (HR) for all-cause mortality per 5 units increment in BMI. (A): HFpEF; B): HFrEF). HR and 95% CI are represented by the black dot and horizontal line, respectively; the area of the grey square is proportional to the specific-study weight to the overall meta-analysis.

Table 1: Baseline characteristics for included studies

Study	Pub Year	Number of patients	Source	Follow-up (years)	HF phenotype	Age (years) Mean (SD)	Women (%)	NYHA class (%)
Haass	2011	4,109	USA	4.1	HFpEF	72	60.4	II/III/IV: 3/9/0
DeShutter	2014	47,866	USA	3.1	HFpEF	61.6 (15.4)	55	-
Kapoor	2010	1,236	USA	1.0	HFpEF	71 (12)	4	-
Padwal	2014#	22,009	MAGGIC	3.0	HFrEF:15,956 patients HFpEF: 6,053 patients	66.8	32	II/III: 46/50
Vest	2015	3,811	USA	6.0	HFrEF	54.1 (11.6)	100	I/II/III/IV: 8/31/59/2
Curtis	2005	7,767	USA & Canada	3.1	HFrEF	64 (11)	24.6	I/II/(III or IV): 14.3/54.5/31.3
Zafrir	2015	630	Israel	3.3	HFrEF	65 (13)	20	III or IV: 53
Clark	2015	1,675	USA	2.0	HFrEF	52.2 (11.6)	22.6	III or V: 79.1
Wu	2009	446	USA	0.8	HFrEF	62.2	27.6	-
McAuley	2007	6,876	USA	7.5	HFrEF	58 (11)	10	-

NYHA class: New York Heart Association functional classification; HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction. # the MAGGIC meta-analysis was based on studies originally reported between 1992 and 2006; data collection will have occurred several years earlier [9].

Table 2: Patients comorbidities and mortalities

Study	HF phenotype	BMI group	IHD (%)	Diabetes (%)	COPD (%)	Hypertension (%)	Blood pressure (mean) (Systolic/diastolic)	Creatinine(mg/ dL)/ eGFR (mean with SD)	All-cause / CV mortality N (%)	Reported natriuretic peptide level
Haass 2011	HFpEF	<23.5 23.5-26.4 26.5-30.9 31.0-34.9 >35.0	-	18 20 27 31 41	10 10 8 9 13	76 87 88 92 92	134/77 135/78 136/71 138/72 137/73	1 (0.3)/68(23) 1(0.3)/73 (23) 1 (0.3)/73 (22) 1(0.4)/72 (23) 1(0.3)/71 (24)	108(32%)/68(20%) 205(24)/124(15) 287(19)/168(11) 151(19)/93(12) 123(21)/74(12) (did not report HR)	Yes
DeShutter 2014	HFpEF	<=30 >30	-	-	-	-	135/73 138/77	-	Did not report CV deaths	No
Kapoor 2010	HFpEF	<20 20-25 26-30 31-35 36-40 41-45 >45	59 61 57 64 61 57 37	33 35 37 57 66 72 59	-	82 86 82 89 90 95 87	Any diastolic dysfunction (%): 67,93,86, 80 85 70 92	Creatinine>1.5 (%): 41 34 37 40 36 51 37	Did not report CV deaths	No
Padwal 2014	HFpEF	<22.5 22.5-24.9 25-29.9 30-34.9 >=35	40 45 48 44 35	11 15 19 28 36	-	32 41 48 61 68	135/75 137/77 139/80 140/80 142/81	-	Did not report CV deaths	No
	HFrEF	<22.5 22.5-24.9 25-29.9 30-34.9 >=35	52 57 59 56 47	13 17 22 31 39	-	25 31 37 49 59	124/74 126/76 129/77 132/79 133/80	-	Did not report CV deaths	No
Vest 2015	HFrEF	18.5-24.99 25-29.99 >=30	46 51 44	17 26 38	-	44 54 66	SBP (media): 104 110 110	-	Did not report CV deaths	No

Curtis 2005	HFrEF	<18.5 18.5-24.9 25-29.9 >=30	61 68 74 63	18 20 29 41	-	40 40 46 59	SBP (mean): 124 124 127 132	1.2 1.3 1.3 1.2	72(45)/45(28) 977(38)/840(33) 998(32)/833(27) 550(28)/473(24) (reported HR)	No
Zafrir 2015	HFrEF	<25.5 25.5-30.4 >30.4	-	34 45 55	-	49 59 70	-	1.40 1.38 1.33	Did not report CV deaths	No
Clark 2015	HFrEF	18.5-24.9 25-29.9 >=30	-	19 28 33	-	32 44 47	-	-	Did not report CV deaths	No
Wu 2009	HFrEF	18.5-24.9 25-24.9 >=30	-	20 25 37	-	55 59 65	135/79 134/80 136/80	Initial/peak creatinine: 1.40/1.45 1.21/1.51 1.32/1.24	Did not report CV deaths	No
McAuley 2007	HFrEF	18.5-24.9 25-29.9 >=30	-	7 11 16	-	38 47 59	130/79 133/82 135/84	-	Reported a negative relation between BMI and CV deaths	No

IHD: Ischaemic heart disease, HFpEF: heart failure with preserved ejection fraction, HFrEF: heart failure with reduced ejection fraction, HR: hazard ratio.

Table 3: Baseline medications

Study	HF phenotype	BMI group	Diuretic (%)	Spirono-lactone (%)	ACE inhibitor / ARB (%)	Beta-blocker (%)	Digoxin (%)	Calcium channel blocker (%)	Lipid-lowering agent (%)	Anti-platelet agent (%)	Statins (%)	Nitrates (%)
Haass 2011	HFpEF	<23.5 23.5-26.4 26.5-30.9 31.0-34.9 >35.0	78 81 82 83 91	20 14 15 14 17	23 23 25 28 28	50 59 59 61 63	20 15 13 14 10	31 36 39 45 46	25 27 33 29 35	52 63 61 58 53	-	
DeShutter 2014	HFpEF	<=30 >30	-	-	-	-	-	-	-	-	-	
Kapoor 2010	HFpEF	<20 20-25 26-30 31-35 36-40 41-45 >45	46 49 52 56 59 78 69	-	38 52 53 57 52 76 59	46 45 45 54 53 59 50	17 21 17 15 8 7 7.4	29 40 37 42 37 41 37	-	-	27 43 47 58 56 54 43	
Padwal 2014	HFpEF	<22.5 22.5-24.9 25-29.9 30-34.9 >=35	76 76 74 81 86	18 17 16 15 20	32 35 36 42 36	25 34 40 43 42	42 35 32 28 25	-	-	-	-	
	HFrEF	<22.5 22.5-24.9 25-29.9 30-34.9 >=35	86 83 83 84 89	28 25 23 25 25	68 72 70 68 65	30 38 42 48 49	59 53 49 46 46	-	-	-	-	
Vest 2015	HFrEF	18.5-24.99 25-29.99 >=30	-	-	91 92 92	63 69 73	69 62 61	-	-	-	-	
Curtis 2005	HFrEF	<18.5 18.5-24.9 25-29.9	94 85 84	-	96 93 93	-	42 41 43	-	-	-	-	42 41 43

		>=30	89		94		44					44
Zafrir 2015	HFrEF	<25.5 25.5-30.4 >30.4	-	-	85 89 89	90 96 94	-	-	-	-	-	-
Clark 2015	HFrEF	18.5-24.9 25-29.9 >=30	31 41 46	-	-	56 64 71	-	-	-	-	-	-
Wu 2009	HFrEF	18.5-24.9 25-24.9 >=30	38 41 40	-	73 76 72	73 84 81	18 17 8	8 6 10	-	-	65 70 73	-
McAuley 2007	HFrEF	18.5-24.9 25-29.9 >=30	-	-	-	15 20 23	-	22 23 26	-	Antihypertensive agent 16 20 23	-	-

IHD: Ischaemic heart disease, HFpEF: heart failure with preserved ejection fraction, HFrEF: heart failure with reduced ejection fraction. ‘ –‘ did not report.

Table 4: Hazard and Odds Ratios for All-cause Mortality by BMI Category for the included studies

	HFpEF			**HFrEF**		
Study	BMI Category	HR/OR (95% CI)	Adjusted covariates	BMI Category	HR/OR (95% CI)	Adjusted covariates
Haass 2011	<23.5 23.5-26.4 26.5-30.9 31.0-34.9 >35.0	1.44 (1.12-1.84) 1.18 (0.9 - 1.4) 1 (1 – 1) 1.07 (0.90-1.41) 1.31 (1.03-1.67)	Age, sex, NYHA class, heart rate, systolic blood pressure, left ventricular hypertrophy, LVEF, cause of HF, hospitalization for HF within the last 6 months, hypertension, myocardial infarction, stroke, COPD and/or diabetes, use of diuretics, digoxin, a calcium-channel blocker, lipid-lowering agents, an ACE-inhibitor, or a beta-blocker, and NT-proBNP.	-	-	-
DeShutter 2014	<18.5 18.5-20 20-25 25-30 30-35 35-40 >40	1.9 (1.6-2.3) 1.5 (1.3 -1.7) 1 (1 - 1) 0.8 (0.7 - 0.9) 0.7 (0.6 - 0.8) 0.8 (0.8 - 1.1) 1.2 (0.9 -1.3)	Left ventricular mass index, age, sex, ejection fraction, and relative wall thickness.	-	-	-
Padwal 2014	<22.5 22.5-24.9 25-29.9 30-34.9 >=35	1.12 (0.8 -1.57) 1 (1 -1) 0.74 (0.56 -0.97) 0.64 (0.46 -0.88) 0.71 (0.49 -1.05)	Age, sex, aetiology (ischaemic or non-ischaemic), hypertension, diabetes and baseline blood pressure	<22.5 22.5-24.9 25-29.9 30-34.9 >=35	1.31 (1.15 -1.5) 1 (1 – 1) 0.85 (0.76 -0.96) 0.64 (0.55 -0.74) 0.95 (0.78 -1.15)	Age, sex, aetiology (ischaemic or non-ischaemic), hypertension, diabetes and baseline blood pressure
Vest 2015	-	-	-	18.5-24.99 25-29.99 >=30	1 (1 -1) 1.08 (1.03 -1.13) 1.09 (1.04 -1.14)	Age, race, ischemic etiology, NYHA, digoxin, ACE inhibitor/ARB, beta-blocker, diabetes, smoking, HTN, hypercholesterolemia, AF, resting SBP, HRR, peak VO2, peak RER, peak Vt, subsequent transplant or LVAD.
Kapoor 2010	<20 20-25 26-30	1.68 (1.04 -2.65) 1.25 (0.92 -1.68) 1 (1 -1)	Age, history, medications, and laboratory and echocardiographic variables.	-	-	-

	31-35 36-40 41-45 >45	0.99 (0.71 -1.36) 0.58 (0.35 -0.97) 0.79 (0.44 -1.4) 1.38 (0.74 -2.6)				
Curtis 2005	-	-	-	<18.5 18.5-24.9 25-29.9 >=30	1.21 (0.95 -1.53) 1 (1 -1) 0.88 (0.8 -0.96) 0.81 (0.72 -0.92)	Age; sex; LVEF; New York Heart Association class; history of myocardial infarction; dyspnea; duration of HF symptoms; diabetes; hypertension; HF etiology; blood pressure; heart rate; rales; elevated jugular venous pressure; peripheral oedema.
McAuley 2007	-	-	-	18.5-24.9 25-29.9 >=30	1 (1-1) 0.70 (0.63-0.79) 0.65 (0.57-0.76)	Age, sex, CVD, smoking, hypertension, hypercholesterolemia, myocardial infarction, stroke or surgery for CVD and metabolic equivalent.
Zafrir 2015	-	-	-	<25.5 25.5-30.4 >30.4	1.11 (0.79-1.55) 1.02 (0.73-1.44) 1 (1-1)	Sex, hypertension, history of myocardial infarction, left ventricular ejection fraction, permanent/paroxysmal atrial fibrillation,left atrial dimension, QRS width, haemoglobin and creatinine level, NYHA grade and beta-blockers.
Clark 2015	-	-	-	18.5-24.9 25-29.9 >=30	Peak oxygen uptake<=14: 1 (1-1) 0.91(0.66-1.25) 0.64 (0.44-0.91); Peak oxygen uptake>14: 1 (1-1) 0.75(0.43-1.32)	Age, diabetes, left ventricular ejection fraction, ACE inhibitor/ARB use, New York Heart Association class, and heart failure etiology (ischemic vs non-ischemic).

					0.87(0.43-1.75)	
Wu, 2009	-	-	-	18.5-24.9 25-24.9 >=30	1 (1-1) 0.63 (0.42-0.94) 1.06 (0.69-1.64)	Sex, age, diabetes, LVEF, blocker prescribed at hospital discharge, angiotensin-converting enzyme inhibitor or angiotensin receptor blocker prescribed at discharge, initial creatinine, and hemoglobin.

HFpEF: heart failure with preserved ejection fraction, HFrEF: heart failure with reduced ejection fraction.

Table 5: The associations between BMI and all-cause mortality by different age groups

	HFrEF				HFpEF			
Age groups	N	HR (95% CI)	I^2 (%)	P-heterogeneity (in the group of studies)	N	HR (95% CI)	I^2 (%)	P-heterogeneity (in the group of studies)
≥60	4	0.95 (0.92-0.97) (p<0.05)	42%	0.16	4	0.93 (0.89-0.97) (p<0.05)	76%	0.006
<60	3	0.97 (0.91-1.03) (p>0.05)	97%	<0.001	0	-	-	-
≥65	2	0.95 (0.91-1.00) (p>0.05)	69 %	0.07	3	0.95 (0.92-0.97) (p<0.05)	0%	0.57
<65	5	0.96 (0.92-1.01) (p>0.05)	95%	<0.001	1	0.89 (0.87-0.91) (p<0.05)	-	-